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<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>			U.S. APPLICATION NO. (If known, see 37 CFR 1.5)  <b>10/031100</b>
INTERNATIONAL APPLICATION NO. PCT/GB00/02664	INTERNATIONAL FILING DATE 11 July 2000 (11.07.00)	PRIORITY DATE CLAIMED 12 July 1999 (12.07.99)	
TITLE OF INVENTION GROWTH HORMONE FORMULATIONS			
APPLICANT(S) FOR DO/EO/US SIEBOLD ET AL.			

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unexecuted Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Application Data Sheet

JG12 Rec'd PCT/PTC 10 JAN 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) <b>107031100</b>	INTERNATIONAL APPLICATION NO <b>PCT/GB00/02664</b>	ATTORNEY'S DOCKET NUMBER <b>G-32210A/GBG</b>
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17. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):</b>					<b>CALCULATIONS PTO USE ONLY</b>	
Search Report has been prepared by the EPO or JPO ..... \$890						
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... \$710						
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$740						
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO. .... \$1,040						
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). .... \$100						
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>					\$ 890	
Surcharge of \$130 for furnishing the oath of declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).					\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE			
Total claims	36 - 20 =	16	X \$ 18	\$ 288		
Independent claims	7 - 3 =	4	X \$ 84	\$ 336		
MULTIPLE DEPENDENT CLAIM(S) (if applicable) + \$ 280				\$ 280		
<b>TOTAL OF ABOVE CALCULATIONS =</b>					\$ 1,794	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).					\$	
<b>SUBTOTAL =</b>					\$ 1,794	
Processing fee of \$130 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					\$	
<b>TOTAL NATIONAL FEE =</b>					\$ 1,794	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property +					\$ 0	
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- a. ☐ A check in the amount of \$\_\_\_\_\_ to cover the above fees is enclosed.
- b. ☒ Please charge Deposit Account No. 19-0134 in the name of Novartis Corporation in the amount of \$1,794 to cover the above fees. A duplicate copy of this form is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134 in the name of Novartis Corporation.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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**GROWTH HORMONE FORMULATIONS**

5 The present invention relates to liquid formulations of growth hormone (GH) suitable for administration to the human or animal body. More particularly, the invention relates to liquid formulations of human growth hormone (hGH) which are pharmaceutically more acceptable and preferable and yet can be subjected to a variety of manufacturing process steps without appreciable loss in activity or appreciable loss of stability.

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Native hGH is a single polypeptide chain protein consisting of 191 amino acids. The protein is internally cross-linked by two disulphide bridges and in monomeric form exhibits a molecular weight of 22kDa. GH of animal species is closely homologous in amino acid sequence to that of humans and is therefore  
15 very similar in its characteristics.

A major biological effect of GH is to promote growth throughout a range of organs and tissues in the body. GH responsive organs or tissues include the liver, intestine, kidneys, muscles, connective tissue and the skeleton.

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Hypopituitary dwarfism is a condition which is readily treated by administering GH to a subject suffering the condition. Prior to the production of large quantities of hGH by recombinant means only limited amounts of hGH could be prepared by laborious extraction of pituitary glands from human cadavers. This  
25 practice carried with it risks associated with infectious agents, eg the agent responsible for Creutzfeldt-Jakob disease (CJD), and that these agents might be passed to the patient receiving GH. The isolation of the hGH gene and the construction of transformed host cells expressing hGH in cell culture has opened up not only a more reliable, safer and more cost effective treatment of  
30 hypopituitary dwarfism, but the possibility of using hGH for treatment of other diseases and conditions as well.

A long appreciated problem with aqueous liquid formulations of pharmaceutical proteins, not just hGH, has been that of instability during storage over a period of time. hGH in aqueous solution is known to undergo a variety of degradative

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changes. Chemical changes such as deamidation occur and this may be related to the pH of the solution during storage. Oxidation of methionine residues may occur. There is also the possibility of a clipping of the peptide backbone occurring due to hydrolysis reactions. Also there are physical changes which may include aggregation for example resulting in the formation of insolubles.

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An early suggestion of how to deal with the problems of instability noted above was freeze drying but this of course meant that the resulting lyophilised product needed reconstitution immediately or shortly prior to administration. In the circumstances of routine self-administration by a patient at home, this normally means that the patient has the task of reconstituting the lyophilised preparation into an aqueous solution. This is inconvenient for the patient and carries with it a risk of improper reconstitution due to lack of care, lack of attention to detail and instructions or simply misunderstanding.

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US 4 968 299 (Kabi Pharmacia) describes a device for a patient to use to perform reconstitution of a lyophilised preparation thereby seeking to lessen the possibility of errors in reconstitution. Even so, the need for reconstitution itself is inconvenient for a patient and the reconstituted hGH is only stable for 3 weeks when stored at 2-8°C. Effective administration by the patient over a period of months still therefore required careful attention to detail and instructions and so there were still serious risks of non-compliance in the treatment regime.

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In any event, freeze drying has the disadvantage of being a costly and time consuming manufacturing step.

Efforts to simplify self-administration for patients have therefore focused on ways of providing sufficiently stable aqueous hGH formulations in a ready to use form.

Protein instability in aqueous solution was appreciated to be a general phenomenon, not one associated particularly with hGH.

- 5 EP-A-0 131 864 (Hoechst Aktiengesellschaft) describes the prevention of aggregation in proteins of greater than 8.5 kDa in aqueous solution by using surfactants.

10 EP-A-0 211 601 (International Minerals & Chemical Corporation) although perhaps primarily concerned with sustained release formulations describes how GH can be stabilised in solution as a liquid by formulating it with non-ionic surfactants, in particular certain polyoxyethylene-polyoxypropylene block copolymers, eg PLURONIC (trade mark of BASF) or GENAPOL (trade mark of Hoechst) block copolymer.

15 WO 94/03198 (Genentech) is another disclosure following the previous teachings about using non-ionic surfactant as an hGH stabiliser in liquid formulations. The range 0.1-5% (w/v) non-ionic surfactant in the formulation is said to permit the formulation to be exposed to shear and surface stresses  
20 without causing denaturation of the GH protein. In particular, the surfactant-containing formulations are seen as being useful in pulmonary dosing and needleless jet injector guns.

25 However, surfactants are toxic substances, and their use should be avoided or at least minimised so far as is possible. This is especially so where formulations are to be administered daily or very frequently, particularly where children and chronic treatments are concerned.

A variety of other ways of stabilising aqueous hGH formulations have been proposed. WO 89/09614 (Genentech) teaches a formulation of hGH comprising  
30 glycine, mannitol and a buffer; there being an hGH:glycine molar ratio of from 1:50 to 1:200.

EP-A-0 303 746 (International Minerals and Chemical Corporation) teaches that aqueous GH may be stabilised by formulating it with a polyol, eg non-reducing sugars, sugar alcohols, sugar acids, lactose, pentaerythritol, water-soluble dextrans and Ficoll; an amino acid, eg glycine, arginine and betaine; an amino acid polymer having a charged side group of physiological pH; and finally a choline derivative, eg choline chloride, choline dihydrogen citrate or dicholine mucate. Many of the polymeric materials referred to above may carry some risk in administration to patients. Pharmaceutical regulatory requirements dictate that any unnecessary additives, particularly synthetic additives (eg pentaerythritol) must be avoided in order to reduce risks to patients. Many of the suggested stabilisers in the disclosure would not appear clinically acceptable and therefore would not enable a pharmaceutically acceptable formulation to be made.

WO 92/17200 (Genentech) is concerned with stabilising hGH, not just in liquid but also in lyophilised preparations. The suggestion is that stable zinc:hGH dimers are produced. The zinc:hGH dimers are made up of two zinc ions and two hGH molecules.

WO 93/12811 (Novo Nordisk) discloses a liquid hGH formulation in which asparagine is used as the stabilising and buffering substance.

WO 93/19776 (Kabi Pharmacia) teaches the totally unexpected finding that when an aqueous hGH product is formulated with citrate buffer then it is more stable than when it is formulated with phosphate buffer.

An object of the present invention is to provide a sufficiently stable hGH formulation instantly usable by patients without the need for any particular preparation or reconstitution procedures. Another object of the invention is to provide a formulation which can be stored at home in a domestic refrigerator for at least a few months. Yet another object of the invention is to provide a bulk

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liquid formulation which can be dispensed and filled into cartridges for patient use without unacceptable losses in GH activity or unacceptable instability, in particular without unacceptable aggregation occurring. A still further object of the invention is to provide a sufficiently stable liquid formulation which avoids or  
5 minimizes the use of pharmaceutically unacceptable or undesirable components, in other words to provide an even more pharmaceutically acceptable formulation.

A yet further object of the invention is to provide liquid formulations which avoid  
10 the problem of crystal formation when stored in the refrigerator for long periods, e.g. up to 6 or 18 months, or if stored for periods of time outside a refrigerator, e.g. periods of several days, weeks or months.

Entirely contrary to the existing wisdom in the art, the present inventors have  
15 surprisingly discovered that it is not actually necessary to employ a variety of additional stabilising agents in solution above and beyond simply hGH and a phosphate buffer in order to achieve the aforementioned objectives. Furthermore, the present invention arises in the face of the prior art teachings about how surfactants are essential for stability of aqueous solutions of GH and  
20 also how phosphate buffered solutions fail to give good stability compared to citrate buffer.

Accordingly, in one aspect the present invention provides a liquid growth hormone formulation consisting essentially of growth hormone in phosphate  
25 buffered solution.

In a second aspect the invention provides a liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution and a preservative.  
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In a third aspect the invention provides a liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution and a preservative.

In a fourth aspect the invention provides a liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution.

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Advantageously, the aforementioned formulations lacking preservative when stored in ampoules provide a convenient way of presenting single shot dosages. For multi-shot dosages the presence of a preservative is preferable.

- 10 A hitherto unappreciated and indeed surprising advantage of all of the aforementioned formulations is that they are storage stable at refrigeration temperatures in the range 2-8°C. A variety of test procedures can be used to assess the stability of formulations over time. Representative examples of test procedures are given in Example 3 herein and also in WO 94/03198
- 15 incorporated herein by way of reference but these procedures are in no way exhaustive or comprehensive of the tests which can be employed to assess stability.

- The filling of dosage containers with growth hormone formulations lacking any
- 20 non-ionic surfactant and using commercially available filling apparatus has been found to result in unacceptable levels of aggregation of growth hormone. However, provided that the fluid pressures and shear stresses are minimised during filling procedures (whether using commercial filling apparatus or not) then surfactant levels can be minimised or dispensed with altogether. The actual
- 25 balance required to be achieved between physical filling stresses and the concentration of surfactant is a matter for routine empirical determination by one of average skill in the art.

- Depending on the levels of physical stresses or shear forces arising during filling
- 30 and where a non-ionic surfactant is needed to avoid significant aggregation then the concentrations of non-ionic surfactant may be as low as about 0.2% (w/v), usually less than 0.05% (w/v), preferably less than 0.04% (w/v), more preferably less than 0.01% (w/v), or even more preferably less than 0.001% (w/v).



Non-ionic surfactants may include a polysorbate, such as polysorbate 20 or 80, etc., and the poloxamers, such as poloxamer 184 or 188, Pluronic® polyols, and other ethylene/polypropylene block polymers.

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Unexpectedly, the inventors have found that phosphate buffer may be used in GH formulations and it is surprisingly good at stabilising the resultant formulations, either during processing such as filling containers, or during storage.

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An absence or use of only a very low concentration of non-ionic surfactant has also surprisingly been found not to adversely affect the stability of GH formulation stored in containers at refrigeration temperatures (in the range 2-8°C for example). Storage for at least three months and longer to at least 6 months or 12 months is possible without unduly affecting the efficacy or pharmaceutical acceptability of the GH formulations.

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In a fifth aspect the invention provides a liquid growth hormone formulation comprising growth hormone in phosphate buffered solution, optionally further comprising a preservative.

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In the aforementioned aspects of the invention, the phosphate buffered solution is preferably isotonic. When the buffered solution is isotonic then the isotonicity may be provided by a neutral salt, eg NaCl; or monosaccharide, eg lactose; a disaccharide eg sucrose or a sugar alcohol, eg mannitol.

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The inventors have also found that certain compounds can be used advantageously in place of neutral salt in order to render the GH formulations isotonic.

Thus, in a sixth aspect the invention provides a liquid growth hormone formulation comprising growth hormone in isotonic buffered solution, optionally phosphate buffered solution, the compound conferring isotonicity being selected

from one or more of monosaccharides, eg lactose; disaccharides, eg sucrose; sugar alcohols, eg mannitol.

- 5 As to the pH, the preferred formulations fall within the range pH 5.0 to 7.0, more preferably pH 5.6 to 6.5.

Surprisingly, and for all formulations described herein, the inventors have found that the problem of crystallisation in formulations can be avoided or minimised  
10 by ensuring a pH of about 6.2 or greater.

Preferably the pH of the formulations is in the range 6.15 to 7.4, more preferably 6.2 to 6.5 to avoid or minimise crystallisation.

- 15 Therefore the invention includes liquid formulations as described herein having no detectable crystallisation on storage. The storage may be at least one month, preferably six weeks, more preferably a period in the range of about 1 month to 4 month, most preferably 3 months. The storage temperature may be about 2°C or greater, preferably about 4°C or greater, more preferably a  
20 temperature in the range from about 2°C to less than 40°C, even more preferably a temperature in the range from about 2°C to 25°C, most preferably 15°C.

The crystallisation is preferably that of growth hormone. Preferably any  
25 crystallisation in the liquid formulation is detected directly by eye, more preferably under the light microscope at 5x magnification, even more preferably under the light microscope at 10x magnification. Prior to observation under the light microscope formulations may be filtered and the presence or absence of crystals on the filter determined. When viewing under the light microscope the  
30 filter may have a pore size of about 5µm.

A particularly preferred test for crystallisation is to store the formulation for 3 months at 15°C and observe the presence or absence of crystals by eye.

As to a preservative this is preferably selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben and benzalkonium chloride although any other preservative or antibacterial compound may be used  
5 at an appropriate concentration such that the formulation remains pharmaceutically acceptable.

In preferred embodiments the phosphate buffered solution is made up of appropriate amounts of appropriate hydrated forms of  $\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$   
10 needed to achieve the desired concentration and pH of buffer, as will be readily recognised and known by one of average skill in the art.

In preferred embodiments the growth hormone is human.

15 In especially preferred formulations, the growth hormone exhibits less than 0.01% aggregation, preferably less than 0.1%, more preferably less than 1%, even more preferably less than 10% aggregation. The aggregation may be measured by the standard size exclusion HPLC test referred to in more detail later but any suitable method of measuring aggregation can be employed.

20 The invention also includes devices for administering a liquid to a subject by injection and loaded for use with at least one dosage unit of any of the liquid growth hormone formulations hereinbefore described. An example of such a device is a pen injector device. The subject is preferably a human.

25 Also provided by the invention are kits comprising an injection device and separate container of any of the liquid growth hormone formulations as hereinbefore described. The container is preferably adapted to engage with the injection device such that in use the liquid formulation in the container is in fluid  
30 connection with the outlet of the injection device.

In particularly preferred embodiments the injection device is a pen injector and the container is a cartridge.

Furthermore, the invention provides a cartridge containing any of the liquid formulations as hereinbefore described for use with a pen injector device.

- 5 Another surprising discovery made by the inventors is that if containers of GH are filled and closed so that there is no airspace or access to the air then not only is sterility of the contents of the containers more reliably assured but that this factor too contributes to minimising or avoiding aggregation of GH.
- 10 Thus, a still further aspect of the invention includes sealed containers of liquid GH formulations in which there is substantially no airspace in the filled containers.

- When the subjects for administration are humans then the preferred growth hormone is human growth hormone. Particularly preferred human growth hormone is produced by recombinant means, for example as taught in EP-A-0 217 822 (SCIOS NOVA). Variants of human growth hormone which may be used in accordance with the invention, alone or in combination with one another and the native hormone include the 191 amino acid species known as somatropin and the 192 amino acid N-terminal methionine (met) species known as somatrem. There is also the variant known as hGH-V found naturally in the placenta during pregnancy and for which the gene is known and recombinant protein has been prepared.
- 15
- 20

- 25 The amount of hGH in the liquid formulation of the invention depends on the volume of the formulation and the number of doses of hGH that volume is intended to provide. A preferred dosage volume is 0.4ml but volumes in the range 0.01ml to 1.0ml may be used. Other preferred dosage volumes may fall in the range 0.1ml to 0.6ml.

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In a preferred unit dosage for daily administration the amount of hGH administered is 1.3mg although the precise dosage amount may vary depending on the particular individual. Dosage amounts in the range 0.033mg to 3.33mg

hGH may be employed, preferably dosages in the range 0.33mg to 2.0mg. Increased dosage amounts are appropriate where the frequency of administration is reduced.

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The volumes and/or dosage amounts may vary from individual to individual in accordance with specific advice from the clinician in charge.

10 Usually, formulations in accordance with the invention may comprise hGH in the range 0.5mg/ml to 20mg/ml, preferably 1mg/ml to 15mg/ml, more preferably 2mg/ml to 10mg/ml, even more preferably 3mg/ml to 5mg/ml.

The invention also includes kits comprising an injection device and a separate container of liquid growth hormone formulation as hereinbefore described.

15 When the administration device is simply a hypodermic syringe then the kit may comprise the syringe, a needle and a vial or ampoule containing the hGH formulation for use with the syringe. In more preferred embodiments the injection device is other than a simple hypodermic syringe and so the separate container is adapted to engage with the injection device such that in use the

20 liquid formulation in the container is in fluid connection with the outlet of the injection device.

Examples of administration devices include but are not limited to hypodermic syringes and pen injector devices.

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Particularly preferred injection devices are the pen injectors in which case the container is a cartridge, preferably a disposable cartridge.

In another aspect the invention provides a cartridge containing a liquid growth formulation as hereinbefore described for use with a pen injector device. The

30 cartridge may contain a single dose or multiplicity of doses of growth hormone.

Preferred embodiments of the invention will now be described by way of the following examples with reference to drawings in which:

- 5 Figure 1 is a plot of comparative stability data at 2-8°C for hGH formulations additionally containing phosphate buffer at pH 5.6, sodium chloride and benzyl alcohol. The comparison is of these formulations with and without Pluronic surfactant. Time in weeks is plotted against log% purity of hGH.
- 10 Figure 2 is a plot of comparative stability data at 2-8°C for hGH formulations additionally containing sodium chloride and benzyl alcohol at pH 6.0. The comparison is of these formulations containing citrate or phosphate buffer. Time in weeks is plotted against log% purity of hGH.
- 15 Figure 3 is a plot of comparative stability data at 2-8°C for hGH formulations. The comparison is between hGH formulations containing isotonic citrate buffer and Pluronic surfactant with hGH formulations containing just isotonic phosphate buffer and no surfactant.

20 **Example 1 - Preparation and purification of bulk recombinant hGH**

- Recombinant hGH is produced in cell cultures of CHO cells transformed with the hGH gene to express the hGH protein under culture conditions. Details of how the cells are made and grown are described in EP-A-0 217 822 (SCIOS NOVA)
- 25 incorporated herein by way of reference. The modification of culture conditions for the growth of cultures on an industrial or commercial scale is well within the abilities of one of average skill in the art.

- Once produced by the cells in culture the hGH needs to be extracted and
- 30 purified into a form suitable for pharmaceutical use. This is carried out according to the procedures described in AU 629177 (University of New South Wales & Garvan Institute of Medical Research) incorporated herein by way of reference.

**Example 2 - Preparation of stable liquid formulation**

- 5 Bulk formulation is prepared by mixing the various components together. The order of mixing of components is not critical. Also, the precise state or form of the various components immediately prior to mixing is not critical either. In preferred ways of preparing the formulation the components are prior to mixing in the most convenient state for mixing and the order and mode of mixing is also
- 10 selected to be the most convenient.

Particularly preferred examples of formulations are given below:

**Formulation I**

15	hGH	3.33mg/ml	(10 IU/ml)
	NaH <sub>2</sub> PO <sub>4</sub>	1.05mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub>	0.17mg/ml	
	NaCl	5.85mg/ml	(ie 0.59% w/v)
20	Benzyl alcohol	9.00mg/ml	(ie 0.9% w/v)
	Water for injection	q.s.	
	pH 6.0		

**Formulation II**

25	hGH	3.33mg/ml	(10 IU/ml)
	NaH <sub>2</sub> PO <sub>4</sub>	1.05mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub>	0.17mg/ml	
30	Water for injection	q.s.	
	pH 6.0		

Formulation III

	hGH	3.33mg/ml	(10 IU/ml)
5	NaH <sub>2</sub> PO <sub>4</sub>	1.05mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub>	0.17mg/ml	
	NaCl	5.85mg/ml	(ie 0.59% w/v)
	water for injection	q.s.	
10	pH 6.0		

Formulation IV

	hGH	3.33mg/ml	(10 IU/ml)
15	NaH <sub>2</sub> PO <sub>4</sub>	1.05mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub>	0.17mg/ml	
	Benzyl alcohol	9.00mg/ml	(ie 0.9% v/v)
	water for injection	q.s.	
20	pH 6.0		

Formulation V

	hGH	3.33mg/ml	(10 IU/ml)
25	NaH <sub>2</sub> PO <sub>4</sub>	1.05mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub>	0.17mg/ml	
	Mannitol	35mg/ml	(3.5% w/v)
	Pluronic F-68	2mg/ml	(0.2% w/v)
30	Benzyl alcohol	9mg/ml	(0.9% v/v)
	Water for injection	q.s.	
	pH 6.0		



Formulation VI

	hGH	3.33mg/ml	(10 IU/ml)
5	NaH <sub>2</sub> PO <sub>4</sub> .2H <sub>2</sub> O	0.85mg/ml	} (ie 10mM phosphate buffer)
	Na <sub>2</sub> HPO <sub>4</sub> .7H <sub>2</sub> O	0.31mg/ml	
	Mannitol	35mg/ml	(3.5% w/v)
	Pluronic F-68	2mg/ml	(0.2% w/v)
10	Benzyl alcohol	9mg/ml	(0.9% v/v)
	Water for injection	q.s.	
	pH 6.2		

The above exemplified formulations were prepared as follows:

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1. A double strength excipient solution is prepared by dissolving all the required excipients in water for injection, and adjusting the pH to that required using molar hydrochloric acid or sodium hydroxide solutions.

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2. The bulk growth hormone solution is placed in a vessel and the excipient solution added with careful stirring.

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3. The pH is readjusted if necessary, and the solution made to final volume. For the filling of cartridges for use with pen injectors the solution is filtered through a sterilising filter and filled into injection cartridges sealed at one end with a moveable plunger, and at the other with an aluminium seal containing a rubber septum.

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Other test formulations were prepared generally in this way and details of these formulations are given in the example below.

**Example 3 - Testing for stability of aqueous hGH formulation**

- Samples of the product were stored under controlled conditions at 2-8°C, and
- 5 analysed at various time points. The stability of the product was determined by the use of two HPLC methods, both according to the European Pharmacopoeia monograph for SOMATROPIN FOR INJECTION, incorporated herein by way of reference. The first is a reverse phase HPLC 4method for the determination of related proteins, ie degradation products formed by deamidation and oxidation.
- 10 The second is a size exclusion HPLC method for determination of dimer and related substances of higher molecular mass.

- The rpHPLC method was used to ascertain deamidation and oxidation of a number of different formulations over a period of up to 65 weeks stored at 2-8°C.
- 15 The data is shown in tables 1 to 3 below and graphically in Figures 1 to 3.

Table 4 shows the results of stability studies carried out on Formulation V stored at 2-8°C.

- 20 The size exclusion HPLC method referred to above (data not shown) was used to test for aggregation. In no case, during the studies were measurable quantities of dimers and related substances of higher molecular mass found. In all formulations there was less than 1% aggregation (in fact this is the limit of reliable quantitation in the test), ie no aggregation was seen.
- 25 The results show clearly that phosphate buffer is better than citrate buffer in terms of stabilising formulations and also that an absence of Pluronic surfactant gives rise to greater stability.

TABLE 1

## Stability Study (2-8°C)

## 5 Formulation A (with pluronic, phosphate buffer, pH5.6)

hGH	3.33 mg/ml
Pluronic	0.8 mg/ml
Phosphate buffer	10mM
Sodium Chloride	5.9 mg/ml
Benzyl alcohol	9 mg/ml

Time weeks	hGH % purity	Log hGH % purity
0	98.90	1.9952
3	98.35	1.9928
9	97.84	1.9905
13	97.05	1.9870
30	96.26	1.9834
$k \text{ day}^{-1} \times 10^4$		-1.253

## Formulation B (no pluronic, phosphate buffer, pH5.6)

hGH	3.33 mg/ml
Phosphate buffer	10mM
Sodium Chloride	5.9 mg/ml
Benzyl alcohol	9 mg/ml

Time (wks)	hGH % purity	log hGH % purity
0	96.28	1.9835
0	95.88	1.9817
4	95.45	1.9798
4	95.80	1.9814
15	95.67	1.9808
15	95.89	1.9818
26	94.46	1.9752
26	93.94	1.9729
39	94.15	1.9738
52	93.21	1.9695
$k \text{ day}^{-1} \times 10^4$		-0.8272

TABLE 2

## Stability Study (2-8°C)

hGH	3.33 mg/ml
Pluronic	0.8 mg/ml
Citrate buffer	10mM
Sodium Chloride	5.9 mg/ml
Benzyl alcohol	9 mg/ml

5

## Formulations C1 and C2 (pH5.6 citrate buffer + pluronic)

time (wks)	hGH+	log hGH+
0	97.89	1.9907
0	97.93	1.9909
4	97.12	1.9873
4	96.80	1.9859
13	95.44	1.9797
13	94.85	1.9770
26	93.19	1.9694
26	93.60	1.9713
52	91.32	1.9606
52	91.06	1.9593
0	97.48	1.9889
0	97.71	1.9899
4	96.93	1.9865
4	96.92	1.9864
13	94.89	1.9772
13	95.38	1.9795
26	92.59	1.9666
26	92.65	1.9668
52	90.69	1.9576
52	91.11	1.9596
k day <sup>-1</sup> X 10 <sup>4</sup>		-1.954

TABLE 3

## Stability Study (2-8°C)

## 5 Formulation D

hGH	3.33mg/ml
Phosphate buffer	10mM, pH6.0
Sodium Chloride	5.9mg/ml
Benzyl Alcohol	9mg/ml

Time Weeks	hGH % purity	log hGH % purity
0	98.47	1.9933
4	97.82	1.9904
9	97.44	1.9887
k day <sup>-1</sup> X 10 <sup>4</sup>		-1.65

## Stability study (2-8°C)

Formulations E1, E2 and E3 (citrate buffer pH6.0, with pluronic)

10 hGH	3.33mg/ml
Pluronic	0.8mg/ml
Citrate buffer	10mM, pH6.0
Sodium Chloride	5.9mg/ml
Benzyl Alcohol	9mg/ml

time (wks)	hGH % purity	log hGH % purity
0	97.75	1.9901
0	97.56	1.9893
5	96.05	1.9825
5	96.95	1.9865
9	96.29	1.9836
9	96.12	1.9828
0	97.96	1.9910
0	97.93	1.9909
5	97.09	1.9872
9	96.52	1.9846
9	96.51	1.9846
0	98.54	1.9936
0	98.47	1.9933
5	97.68	1.9898
5	97.43	1.9887
9	96.67	1.9853
9	96.77	1.9857
k day <sup>-1</sup> X 10 <sup>4</sup>		-2.55

TABLE 4

Stability study; Formulation V, 2-8°C

Time Weeks	hGH % purity	log hGH % purity
0	97.21	1.988
0	97.23	1.988
4.5	96.50	1.985
4.5	96.65	1.985
9	95.18	1.979
9	95.19	1.979
13	95.23	1.979
13	95.32	1.979
26	94.64	1.976
26	94.41	1.975
k day <sup>-1</sup> X 10 <sup>4</sup>		-2.489

5

**Example 4 – Avoidance of crystallisation by pH adjustment of liquid formulations**

10 A series of pH variants (0.1 unit increments) of formulation VI were made by adjusting the respective amounts of the phosphate buffer components. 1.5ml aliquots of the formulations were filled into respective capsules for use in pen injectors. The capsules were stored at 15°C for up to 3 months. The presence or absence of crystals in the capsules was determined by eye over the storage period.

15

Crystallisation was observed in formulations of below pH 6.2, i.e. at pH 6.1. No crystallisation was observed in formulations of pH 6.2 and above.

20 By way of comparison, formulation V (pH 6.0) when stored at 15°C or 25°C for up to 6 weeks exhibited crystallisation. Also, formulation V (pH 6.0) exhibited crystallisation in about 2-3 months when stored at 2-8°C.

**Claims**

1. A liquid growth hormone formulation comprising growth hormone in isotonic buffered solution, the compound conferring isotonicity being selected  
5 from one or more of monosaccharides, disaccharides and sugar alcohols.
2. A liquid formulation as claimed in claim 1, wherein the buffered solution is a phosphate buffered solution.
- 10 3. A liquid formulation as claimed in claim 1 or claim 2, wherein the isotonicity is conferred by mannitol and/or sucrose, optionally lactose.
4. A liquid formulation as claimed in any of claims 1 to 3 having a pH in the range 5.6 to 6.5.  
15
5. A liquid formulation as claimed in any of claims 1 to 3 having a pH of 6.2 or greater than about 6.2.
6. A liquid formulation as claimed in any of claims 1 to 4 having a pH in the  
20 range 6.15 to 7.4 more preferably a pH in the range 6.2 to 6.5.
7. A liquid formulation as claimed in any preceding claims further comprising a preservative.
- 25 8. A liquid formulation as claimed in claim 7, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.
9. A liquid formulation as claimed in any preceding claim further comprising  
30 a non-ionic surfactant.

10. A liquid formulation as claimed in claim 9, wherein the non-ionic surfactant is present at a concentration in the range 0.05% to 5% (w/v), preferably 0.1 to 1.0% (w/v).

5

11. A liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution.

12. A liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution and a preservative.

10

13. A liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution and a preservative.

14. A liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution.

15

15. A liquid growth hormone formulation comprising growth hormone in phosphate buffered solution.

20

16. A liquid formulation as claimed in claim 15, further comprising a non-ionic surfactant in a concentration of less than 0.05%, preferably less than 0.04%, more preferably less than 0.01%, even more preferably less than 0.001% (w/v).

17. A liquid formulation as claimed in claim 15 or claim 16, wherein the phosphate buffered solution is isotonic, optionally with a pH in the range 5.6 to 6.5 and preferably further comprising a preservative.

25

18. A liquid formulation as claimed in claim 17, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.

30



19. A liquid formulation as claimed in any of claims 13, 14 or 17, wherein the isotonicity of the phosphate buffered solution is provided by a neutral salt eg NaCl; or a compound selected from a monosaccharide, eg lactose; a  
5 disaccharide, eg sucrose; or a sugar alcohol, eg mannitol.

20. A liquid formulation as claimed in any preceding claim, wherein the growth hormone is human.

10 21. A liquid formulation as claimed in any preceding claim in which the growth hormone exhibits less than 0.01% aggregation, preferably less than 0.1%, more preferably less than 1%, even more preferably less than 10% aggregation.

22. A liquid growth hormone formulation of the following composition:

15	hGH	3.33mg/ml	(10 IU/ml)
	NaH <sub>2</sub> PO <sub>4</sub> .2H <sub>2</sub> O	0.85mg/ml	
	Na <sub>2</sub> HPO <sub>4</sub> .7H <sub>2</sub> O	0.31mg/ml	
	Mannitol	35mg/ml	(3.5% w/v)
	Pluronic F-68	2mg/ml	(0.2% w/v)
20	Benzyl alcohol	9mg/ml	(0.9% v/v)
	Water for injection	q.s.	
	pH 6.2		

23. A liquid formulation as claimed in any preceding claim having no  
25 detectable crystallisation on storage.

24. A liquid formulation as claimed in claim 23, wherein storage is for at least one month, preferably six weeks, more preferably a period in the range of about 1 month to 4 months, most preferably 3 months.

30

25. A liquid formulation as claimed in claim 23 or claim 24, wherein the storage temperature is about 2°C or greater, preferably about 4°C or greater, more preferably a temperature in the range from about 2°C to less than 40°C,

even more preferably a temperature in the range from about 2°C to 25°C, most preferably 15°C.

5 26. A liquid formulation as claimed in any of claims 23 to 25, wherein the crystallisation is of growth hormone.

27. A liquid formulation as claimed in any of claims 23 to 26, wherein the crystallisation is detected by eye, preferably under the light microscope at 5x  
10 magnification, more preferably under the light microscope at 10x magnification.

28. A device for administering a liquid to a subject by injection and loaded for use with at least one dosage unit of the liquid growth hormone formulation of any of claims 1 to 27.

15 29. A device as claimed in claim 28 being a pen injector device.

30. A device as claimed in claim 28 or claim 29, wherein the subject is a human.

20 31. A kit comprising an injection device and a separate container of a liquid growth hormone formulation of any of claims 1 to 27.

32. A kit as claimed in claim 31, wherein the container is adapted to engage  
25 with the injection device such that in use the liquid formulation in the container is in fluid connection with the outlet of the injection device.

33. A kit as claimed in claim 32, wherein the injection device is a pen injector and the container is a cartridge.

30 34. A cartridge containing a liquid formulation of any of claims 1 to 27 for use with a pen injector device.

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

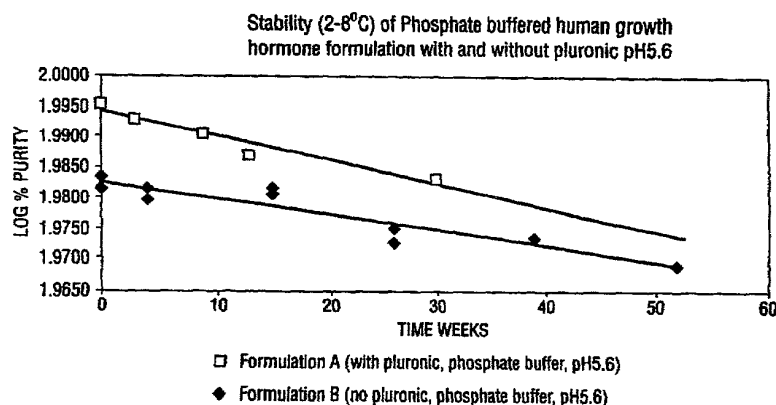
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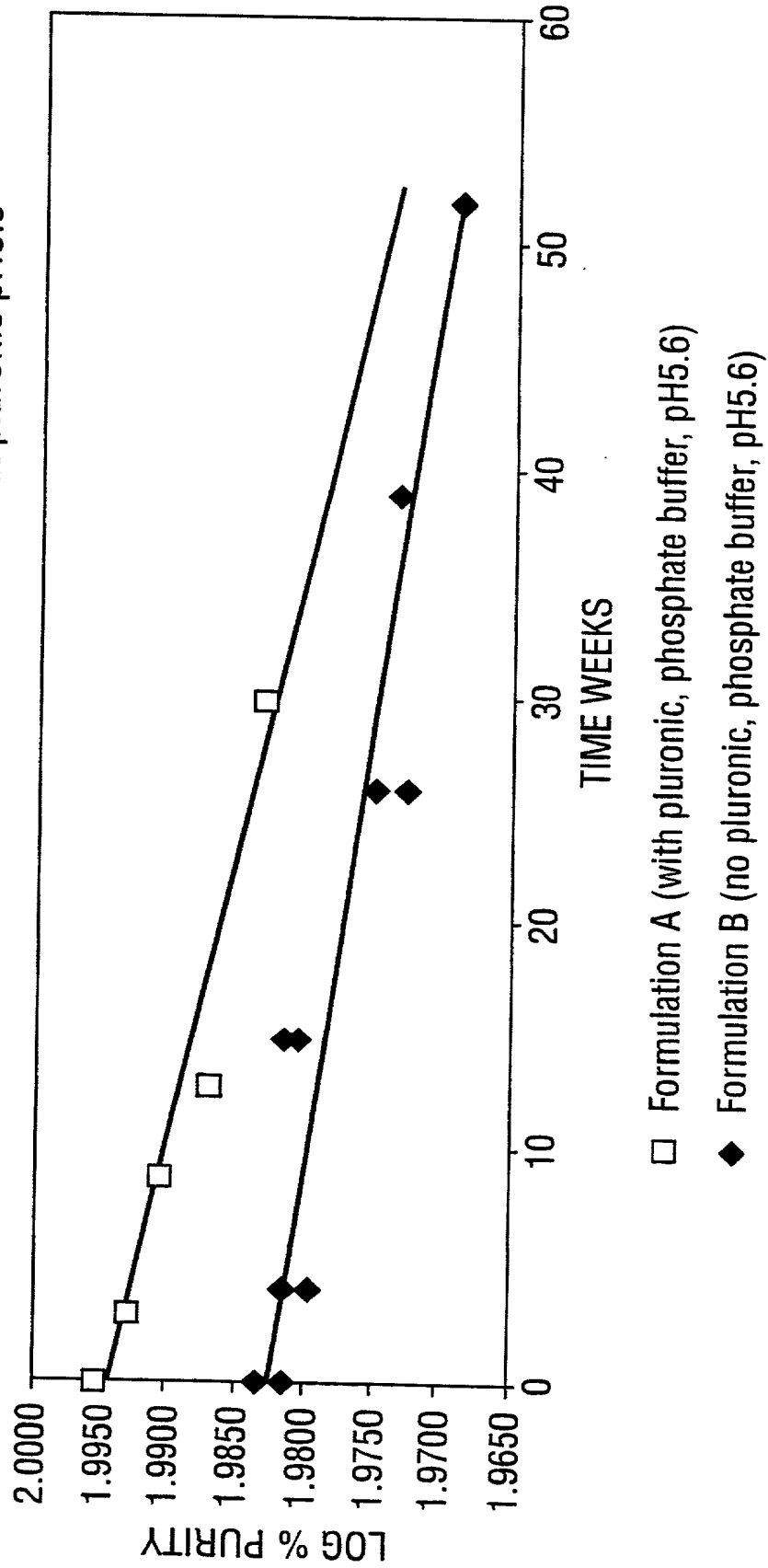


(57) Abstract: Liquid growth hormone formulations are storage stable for more than six months at temperatures in the range 2-8 °C by simply formulating growth hormones in phosphate buffer with no other additives at around physiological pH. By ensuring a pH of about 6.2 or greater, growth hormone crystallisation during storage at refrigeration temperatures or above is inhibited or reduced. Low concentrations of non-ionic surfactant can help to reduce aggregation of growth hormone arising as a result of physical forces encountered during automated transfer of bulk formulation into dosage containers. Mannitol is included in order to provide an isotonic formulation. Preservatives are included to reduce bacterial contamination and thereby permit multiple dosage units which can be stored at 2-8 °C.

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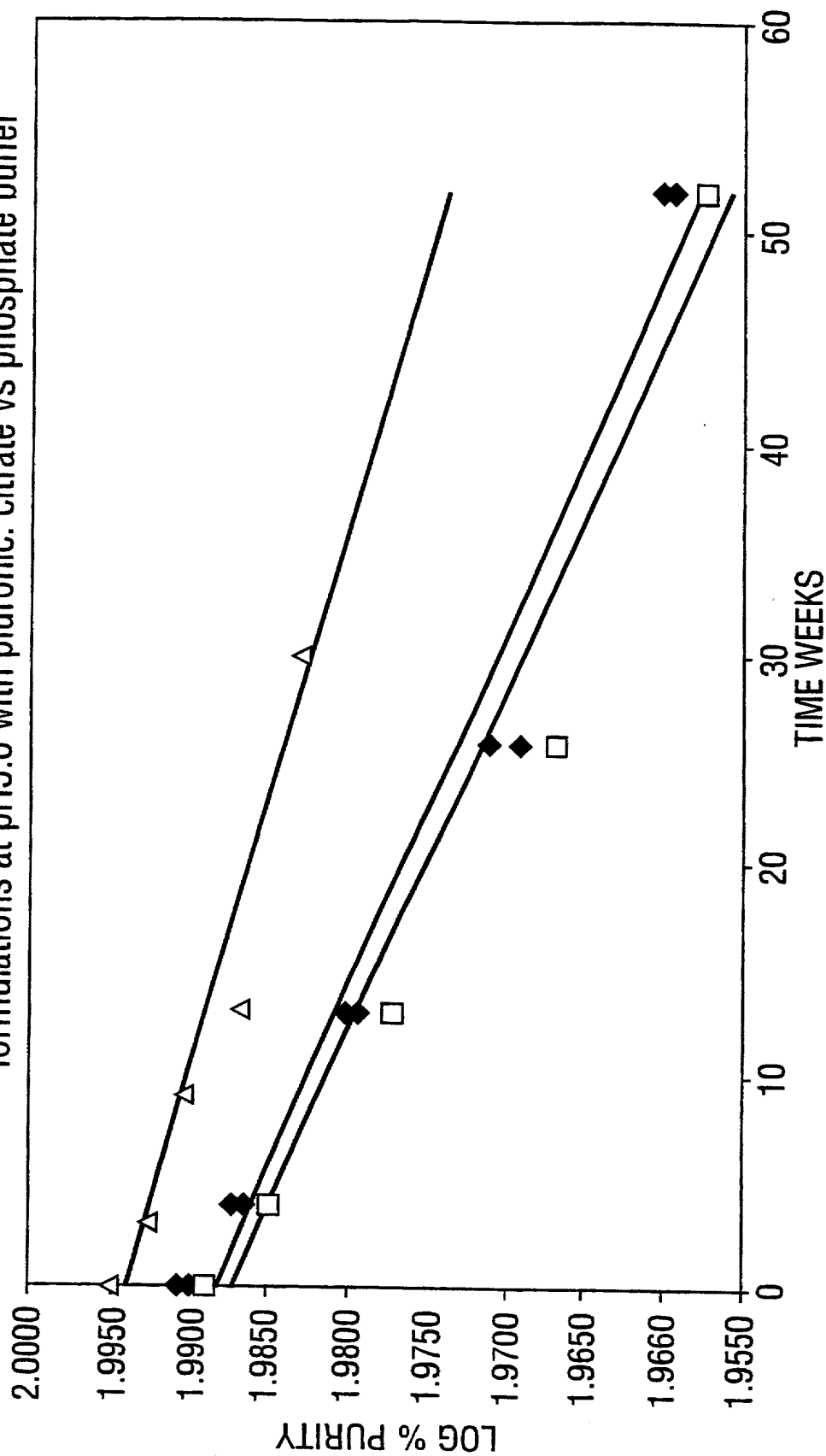
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**FIG. 1** Stability (2-8°C) of Phosphate buffered human growth hormone formulation with and without pluronic pH5.6



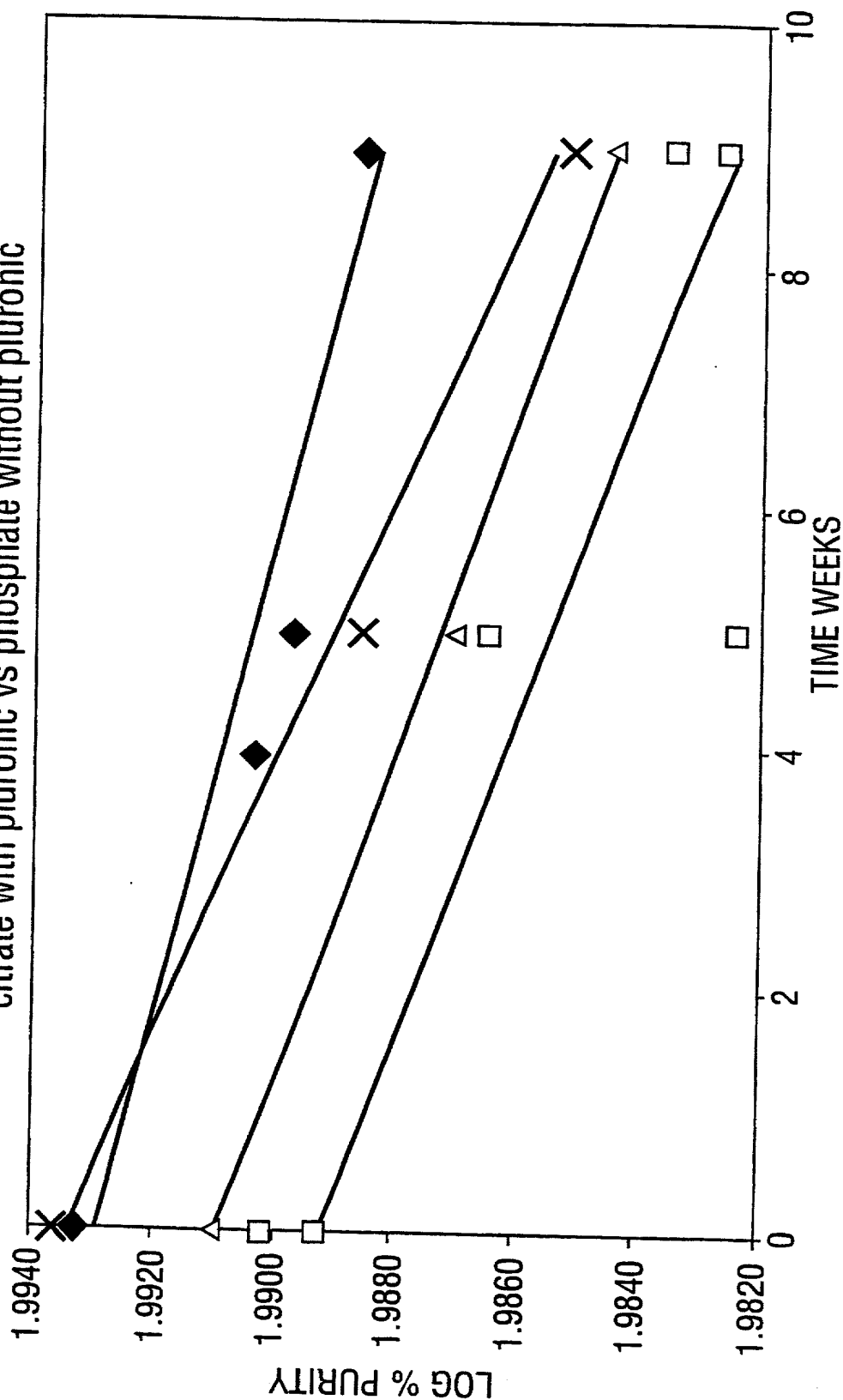
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**FIG. 2** Stability (2-8°C) of buffered human growth hormone formulations at pH5.6 with pluronic: citrate vs phosphate buffer



△ Formulation A (with pluronic, phosphate buffer, pH5.6) ◆ Formulation C2 (with pluronic and citrate buffer, pH5.6)  
□ Formulation C1 (with pluronic and citrate buffer, pH5.6)

**FIG. 3** Stability (2-8°C) of growth hormone formulation (pH6.0), citrate with pluronic vs phosphate without pluronic



- ◆ Formulation D (no pluronic, phosphate buffer, pH6.0)
- Formulation E1 (with pluronic and citrate buffer, pH6.0)
- △ Formulation E2 (with pluronic and citrate buffer, pH6.0)
- × Formulation E3 (with pluronic and citrate buffer, pH6.0)

**DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION**

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

**GROWTH HORMONE FORMULATIONS ✓**

the specification of which:

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**PCT/GB 00/02664** ✓ on **11/07/2000** ✓  
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Great Britain —	9916252.1 —	12/07/1999 —	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Great Britain —	9918902.9 —	12/08/1999 —	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-02  
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Bernhard SIEBOLD

Inventor's signature

Bernhard Siebold

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Citizenship

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Full name of second  
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☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

**GROWTH HORMONE FORMULATIONS**

the specification of which:

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☐ was filed on \_\_\_\_\_ as Application No. \_\_\_\_\_  
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			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No

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I hereby appoint the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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Full name of sole  
or first joint inventor **Bernhard SIEBOLD**

Inventor's signature \_\_\_\_\_ Date \_\_\_\_\_  
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Residence **Kundl, Austria**

Citizenship **German**

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Austria**

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2-05 Full name of second  
joint inventor, if any

John STEVENS

Inventor's signature

John Stevens

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(day/month/year)

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